PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-15172	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/23269	International filing date *(day/month/year)* 18.08.2003	Priority date *(day/month/year)* 23.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/5375		
Applicant ELI LILLY AND COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
02.03.2004	17.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Johnson, C Telephone No. +49 89 2399-8287

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/23269

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-73 as originally filed

Claims, Numbers

1-18 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 12,14-17

   because:

   ☒ the said international application, or the said claims Nos. 12,14-17 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11,13,18
	No:	Claims	

2. Citations and explanations

see separate sheet

III. Non-establishment of opinion

Claims 12, 14-17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

IV. Lack of unity

In order for a group of compounds to fulfill the requirements of Article 13 PCT, all the compounds must possess the same or corresponding special technical features, such features being the characteristics which distinguish them from the closest prior art.

In the present case, the common structure shared by the all the compounds of formula (I) consists of a morpholine ring substituted at the 2-position by a CH-heteroatom-Ar group, wherein the CH moiety is further substituted by a hydrocarbon group and wherein the stereochemistry at the 2 chiral centres is S,S. However, compounds possessing such a structure and having selective norepinephrine reuptake inhibitory activity are already known, see S,S-reboxetine cited in the present description. Thus neither the common structure, nor the activity, nor a combination of the two can form the special technical feature required by Article 13 PCT, as they are already known.

The application thus appears to contain at least 2 non-unitary groups of inventions:

Invention 1: claims 1(part),2-7,8-18(part)

Compounds of formula (I) wherein A is sulfur, their pharmaceutical compositions, uses and methods of preparation. The special technical feature is the sulfur A group.

Invention 2: claims 1(part),8-18(part)

Compounds of formula (I) wherein A is oxygen, their pharmaceutical compositions, uses and methods of preparation. The special technical feature is the X group.

V. Reasoned statement

Reference is made to the following documents:

D1: GB-A-1295447

D2: GB-A-2167407

D3: GB-A-1412546

Examination of invention 1: claims 1(part), 2-7, 8-18(part) relating to

compounds of formula (I) wherein A is S.

Novelty
The present compounds differ from those of D1 and D2 because of the sulfur A group and from those of D3 because the X group cannot be H.
Claims 1-18 fulfil the requirements of Article 33(2) PCT.

Inventive step
D1-D3 concern compounds for use in the treatment of i.a. depression. D1 and D3 do not mention the mechanism of action of the compounds disclosed therein. Reboxetine, disclosed in D2, is known to be a potent and selective inhibitor of the norepinephrine transporter (NET). The technical problem underlying the present claims appears to be the provision of further selective inhibitors of the NET for the treatment of depression. Reboxetine of D2 is taken as the closest prior art. The problem has been solved by replacing the O atom of this prior art compound by an S atom. In the absence of any document disclosing structurally similar inhibitors of the NET showing that the oxygen of the phenoxy substituent may be replaced without loss of activity, those of the present phenoxy derivatives which have the alleged selective NET inhibition activity may be considered inventive.
Claims 1-18 fulfil the requirements of Article 33(3) PCT.

Examination of invention 2: claims 1(part), 8-18(part) relating to compounds of formula (I) wherein A is O.

Novelty
The present compounds differ from those of D1 because of the stereochemical configuration, from those of D2 because of the identity of the X group (see the proviso at the end of claim 1) and from those of D3 because of the identity of both the A and X groups.
Claims 1 and 8-18 fulfil the requirements of Article 33(2) PCT.

Inventive step
D1-D3 concern compounds for use in the treatment of i.a. depression. D1 and D3 do not mention the mechanism of action of the compounds disclosed therein. Reboxetine, disclosed in D2, is known to be a potent and selective inhibitor of the norepinephrine transporter (NET). The technical problem underlying the present claims appears to be the provision of further selective inhibitors of the NET for the treatment of depression. Reboxetine of D2 is taken as the closest prior art. The

problem has been solved by replacing the phenyl group in reboxetine by an alkyl, cycloalkyl or alkylene-cycloalkyl group. In the absence of any document disclosing structurally similar inhibitors of the NET showing that the phenyl group of reboxetine may be replaced without loss of activity, those of the present thiophenyl derivatives which have the alleged selective NET inhibition activity may be considered inventive.

Claims 1 and 8-18 therefore fulfil the requirements of Article 33(3) PCT.

Industrial applicability (of both inventions)

Claims 1-11, 13, 18 fulfil the requirements of Article 33(4) PCT.

No unified criteria exist in the PCT Contracting States for assessing whether present claims 12, 14-17 are industrially applicable. The patentability can be dependent upon the formulation of the claims. For example, the EPO does not consider claims to the use of a compound in medical treatment to be industrially applicable, but allows claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.